ASBMT American Society for Blood and Marrow Transplantation

Re: An Approach to Predicting HSCT Outcome Using HLA-Mismatch Information Mapped on Protein Structure Data

We wish to comment on 3 aspects of the recently published article by Dudkiewicz et al [1]: (1) Table 1, which erroneously summarizes current practice in donor selection; (2) our concerns about the analyses attempting to validate the recommendations in Table 1; and (3) the use of contact energy calculations to predict immunogenicity of specific HLA mismatches.

First, the guidelines listed in Table 1 are not supported by the referenced 3 articles [2-4] published by the National Marrow Donor Program (NMDP) and Center for International Blood and Marrow Transplant Research (CIBMTR). Furthermore, the authors did not cite an update to the NMDP matching guidelines published by Bray et al. [5] (free full text available online), which incorporates the more recent findings by Lee et al. in 2007 [4].

Second, the authors' misrepresentation of the donor matching recommendations confounds their validation assessment because they are not testing current best practices. Dudkiewicz et al. also were not able to adjust for the numerous other clinical variables known to influence transplant outcome beyond HLA matching (disease, disease stage, patient age, cytomegalovirus [CMV] status, etc.). Our corrections to the guidelines listed in Table 1.

Finally, we look forward to learning more about the contact energy calculations used to predict immunogenicity of specific HLA mismatches. However, based on the methods and data presented in this article, we question the authors' conclusions. The authors chose to highlight 2 particular mismatches, HLAB*3501-HLAB*3503 and HLAB*2702-HLAB*2705, because they were the 2 most numerous groups in the database. However, Figure 9, showing the survival curves for these 2 groups, is based on a total of 18 patients (4% of all mismatches in the database), and not adjusted for any clinical characteristics. Conclusions based on such a small number of cases are questionable because small population imbalances can have dramatic effects.

We appreciate the opportunity to comment on the manuscript, and caution readers to refer to the most recent donor selection recommendations [5].

Table 1. Corrections to the donor selection guidelines listed in the article by Dudkiewicz et al [1].

Statements from Dudkiewicz et al [1]	Results in cited NMDP publications
Search for 10/10 match at 5 loci (HLA-A, B, C, DR, and DQ)	Both the Flomenberg et al. [2]and Lee et al. [4] studies show that 8/8 matching (HLA-A, B, C, and DRB1) was the minimum level of matching associated with highest survival; DQ mismatches did not have a significant impact on outcome.
Allele mismatch is less harmful than antigen mismatch	The Flomenberg et al. [2] study suggested that allele mismatches had less of an impact on outcome; however, the later and larger NMDP study by Lee and colleagues[4] showed that both types of mismatches had an indistinguishable impact on outcome. This was discussed in the updated guidelines published by Bray et al. [5].
Chose a donor with a mismatch in HLA-A over a mismatch in HLA-B	In the Lee [4] study, single mismatches at HLA-A appeared to be more poorly tolerated than at HLA-B and HLA-C, but the limited number of transplants with isolated mismatches at HLA-B or HLA-C suggested that more research was needed.
Chose a mismatch with a lower number of amino acid substitutions between alleles	None of the NMDP publications cited addressed the impact of the number of amino acid substitutions on outcome; however, the results of the Lee et al. study [4] related to antigen versus allele differences suggest that the number of amino acids that differ do not have an impact on outcome. In fact, other published studies, some supported by the NMDP, did not find any evidence for selecting an allele with a lower number of amino acid substitutions [6,7]
If there are 2 1-mismatch donors with single amino acid substitution in the same locus, choose the donor with the substitution outside the binding groove	None of the NMDP publications cited addressed the impact of amino acid differences outside of the antigen binding site. A study by Xiao et al. [8] (published after Dudkiewicz et al. [1] submitted their study) indicated that it would not be possible to analyze the impact of these differences with the current number of transplants.
Because graft-versus-host disease (GVHD) may increase the risk of hematopoietic stem cell transplant (HSCT)-related mortality, avoid mismatches that could lead to GVHD	The NMDP guidelines for matching published by Bray et al. [5] state that the impact of HLA matching on survival should be of primary importance. The effect of mismatching on GVHD, treatment-related mortality (TRM), and rejection should be considered in the development of a risk-adapted treatment strategy.

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Cyclosporine Dose Intensity and Risk of Acute Graft-versus-Host Disease: Trough versus Area under the Curve

Malard et al. [1] reported their observation of an inverse correlation between cyclosporine (CsA) concentrations within the first 2 weeks after hematopoietic stem cell transplantation (HSCT) and the severity of acute graft-versus-host disease (aGVHD). CsA was given first as a continuous i.v. infusion and then orally in patients able to receive oral medication. CsA concentrations are referred to as "trough" concentrations, with no distinction made with respect to route of administration (continuous i.v. infusion vs oral). The proportions of patients receiving i.v. and oral doses each week after HSCT are not stated.

When doses are given on an intermittent schedule, trough drug concentrations are obtained at the end of a dosing interval and before administration of the next dose. In contrast, drug concentrations can be determined at any time during a continuous infusion. They can be either steady-state or non–steady-state concentrations, depending on how long the infusion rate is maintained. Ideally, steady-state concentrations, whether drawn at the end of a dosing interval or during a continuous i.v. infusion, are used to describe the relationship between a drug concentration and a clinical endpoint. In any case, drug concentrations obtained during continuous i.v. infusion do not meet the definition of a trough concentration.

In centers where CsA is given by intermittent i.v. infusion, trough whole blood concentrations are used to individualize doses. Similar to the findings of Malard et al., we reported that in 87 children undergoing myeloablative HSCT, higher trough CsA concentrations during the week before engraftment significantly reduced the odds of developing severe aGVHD (univariate analysis, $P = .0409$; multivariate analysis adjusted for type of HSCT, $P = .0454$) [2]. The majority of the children (84 of 87) received a bone marrow transplant, and the median day of engraftment was day +18 (mean, day +19.2; range, day +11 to day +35). Therefore, for many children, the week before engraftment coincided with the second week posttransplantation.

Malard et al. [1] raised the question of whether area under the curve (AUC) rather than trough concentration might be a more effective parameter on which to base CsA dosing. Concentrations determined at steady state in patients receiving continuous CsA i.v. infusion can be used to estimate the AUC. Determination of AUC after intermittent i.v. infusion traditionally requires multiple concentration-time points obtained during the dosing interval. We have developed a limited sampling strategy for determining CsA AUC after a 2-hour CsA